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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,176	11/24/2003	Tariq M. Rana	20336-00016	3047

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
08/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,19-28,30 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,19-28,30 and 33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/23/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 05/23/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 02/26/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 05/23/2008, claims 14, 19-28, 30 and 33-44 are pending and currently under examination in the application.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 05/23/2008 is in compliance with 37 CFR 19.7. The information disclosure statements have been considered by the examiner and signed copies have been placed in the file.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 102

The rejection of claims 14, 20, 22-24 and 43 under 35 U.S.C. 102(e) as being anticipated by Frecht et al. (U.S. Patent No. 7,097,856) is withdrawn.

The rejection of claims 14, 19, 38, 39 and 43 under 35 U.S.C. 102(b) as being anticipated by Szoka et al. (US Patent No. 5,661,025) is maintained for the reasons of record in the office action mailed 02/26/2008.

Applicant's arguments in the response filed 05/28/2008 are acknowledged but not found persuasive. Applicant argues there is no rationale to show that the molecules taught by Szoka et al. are necessarily capable of mediating RNAi and the burden should not shift to Applicant to establish the molecules of Szoka et al. are capable of mediating RNAi. Applicant acknowledges that the molecules taught by Szoka et al. "may be capable of mediating RNAi" but not that the molecules mediating RNAi necessarily flow from the teaching of Szoka et al. Applicant further argues that Szoka et al. do not demonstrate an "effective delivery mixture comprising a generation 2 to 5 dendrimer mixed with a nucleic acid to deliver an active nucleic acid to cells and relies on several additional journal articles for support that the dendrimer mixture is not effective. Applicants cites Haensler and Szoka (see page 6 of the remarks filed 05/23/2008) to reason that the dendrimer mixtures was not effective because it was later found that the dendrimers cited in the Szoka et al. references of record "exhibit only low levels of transfection" and further cite a review article by Eichman (see page 6 of the remarks filed 05/23/2008) as support that the exact structures accounting for the observed results of enhanced transfection activity are still unknown.

In response to Applicant's argument that molecules taught by Szoka et al. do not necessarily mediate RNAi, the burden does in fact shift to Applicants to show that the molecules are not capable of mediating RNAi (See MPEP 2112). The claims are

drawn to a nucleic acid capable of mediating RNAi which can encompass any RNA or DNA molecule, duplex or hybrid molecule of any size. The breadth of claim 14 is further demonstrated by the fact that Applicant further limits the claim to RNA in claim 19 and to miRNA, shRNA or siRNA in claims 21-23. The claims do not recite any size limitation and a nucleic acid capable of mediating RNAi is not defined in the specification in a way to inform one of skill in the art that any of the above cited molecules are excluded from the claim. Szoka et al. teach DNA and RNA molecules, double stranded DNA molecules, hairpin loop RNA molecules and RNA:DNA hybrid molecules and Applicant has not provided any evidence that these molecules do not necessarily possess the function of mediating RNAi.

Applicant's argument that Szoka et al. do not teach an effective delivery mixture comprising a generation 2 to 5 dendrimer mixed with a nucleic acid to deliver an active nucleic acid to cells is not convincing. Szoka et al. teach generation 2 to 5 dendrimers were able to deliver nucleic acid molecules to cells. The claims are not limited to any particular efficiency of transfection of the mixture or any particular activity of the nucleic acid being delivered. The references relied on by Applicant and discussed above, regardless of what further studies were conducted, do not refute the fact that Szoka et al. teach a delivery mixture of generation 2 to 5 dendrimers which can be mixed with nucleic acids as recited above.

Thus, the rejection if maintained.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 14, 19-28, 30 and 33-44 under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (Clinical Cancer Research 2001), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) Olejnik et al. (cited on PTO Form 892 filed 08/23/05) and Grigoriev et al. (cited on PTO Form 892 filed 08/23/05) and evidenced by Milhem et al. (International Journal of Pharmaceutics 2000, Vol. 197: 239-241) is maintained for the reasons of record in the prior office action mailed 02/26/2008.

Applicant's arguments in the response filed 05/28/2008 are acknowledged but not found persuasive. Applicant argues that the assertion of obviousness relies on the finding that one of ordinary skill in the art would have selected a generation 4 dendrimer as a preferred delivery agent from the teaching of Sato et al. for delivery of alternative nucleic acids. Applicants submit that one of skill in the art would not have selected a generation 4 dendrimer as a preferred delivery agent and argue that Sato et al. does not provide evidence of effective delivery of oligonucleotides to cells to confer antisense activity. Applicant argues that in vivo targeting of antisense oligonucleotides is unpredictable and therefore one of skill in the art would recognize that at the time of filing it would not have been obvious to use a dendrimer, particularly a generation 4 dendrimer, to deliver a nucleic acid. Applicants further argue that a person skilled in the art would require more than routine optimization to arrive at a delivery mixture as claimed. Applicants further argue that the teachings of the art at the time of filing, including Sato et al. amount to a teaching away from the use of generation 2 to 5

dendrimer for delivery of nucleic acid conferring siRNA activity and do not support a finding of obviousness. Applicants further state that the remaining references, either alone or in combination with Sato et al. provide any teaching to lead one skilled in the art to produce a delivery mixture as claimed.

Applicant's arguments regarding Sato et al. are not convincing. Sato et al. teach a generation 4 dendrimer, that when mixed with an antisense oligonucleotide, can efficiently deliver said oligonucleotide to cells in vitro and in vivo. The reliance on Sato et al. was not for a teaching of whether or not the reference taught efficient antisense activity against any particular target in the gene. Moreover, the instant claims do not require any activity of the nucleic acid being delivered. The claims are drawn to a delivery mixture wherein the nucleic acid is "capable of mediating RNAi". The claims do not require the nucleic acid being delivered actually confer any RNA interference. Further, even if the claims had such a limitation, there is nothing in the Sato et al. reference that would discourage one of skill in the art away from the use of a generation 4 dendrimer to deliver nucleic acids. Sato et al. teach dendrimers form very stable complexes with negatively charged nucleic acids, are less cytotoxic and are efficient at delivering nucleic acids even in the presence of serum proteins in cells by protecting the nucleic acid from degradation by exonucleases. Given that Sato et al. teach efficient delivery of nucleic acids that were mixed with a generation 4 dendrimer, one of skill in the art would want to use such an efficient delivery mixture for delivery of nucleic acids capable of mediating RNAi since it was well known at the time of filing that RNAi was proving to be more efficient at silencing gene expression.

Applicant's arguments that the delivery of antisense oligonucleotides is "unpredictable" and the teachings of Sato et al. would "require more than routine optimization to arrive at a deliver mixture" are not part of the requirement for the combination of the prior art reference to be obvious over the claimed invention. Further, there is no requirement that "[m]aintenance of an obviousness rejection requires no more than routine testing". Applicant appears to argue that for the claimed invention to be obvious, the prior art references must be enabled and that because Sato et al. does not show that the delivered antisense oligonucleotide actually had any activity against a target gene, one of skill in the art would not want to try to deliver nucleic acids capable of mediating RNAi using the delivery mixture comprising a generation 4 dendrimer taught by Sato et al. Applicant's arguments are not convincing. The instant claims do not require any activity of the nucleic acid being delivered and as stated above, the reliance on Sato et al. was not for a teaching of whether or not the reference taught efficient antisense activity against any particular target gene. Sato et al. teach efficient delivery of nucleic acids across cell membranes and into cells and tissues. It was well known at the time of filing of the instant invention and the field of therapeutic applications using nucleic acids was replete with references discussing the difficulties of delivering nucleic acids to cells which ranged from the toxicity of viral delivery systems, inefficient delivery of nucleic acids to cells and tissues and degradation of nucleic acids by serum proteins found in the cell. Sato et al. has shown very specifically that a generation 4 dendrimer can help to overcome some of the disadvantages of delivering nucleic acids to cells, therefore a person of ordinary skill in the art would have good

reason to use such a delivery agent to deliver nucleic acid that were capable of mediating RNAi and would have expected to be able to deliver the nucleic acids to cells and tissues.

Further, the teachings of Sato et al. in combination with the other references cited by Applicant do not amount to a teaching away as stated. There is no direct statement or conclusion by Sato et al. that would discourage one of skill in the art away from using the generation 4 dendrimer. Sato et al. concludes that said dendrimer have been shown to effectively delivery oligonucleotides and "these complexes have great potential for modification and can be a vector for a variety of oligonucleotides." (see page 3611, last paragraph). One of skill in the art would certainly want to try to delivery mixture taught Sato et al.

Applicant cites the work of Haensler, Szoka and Tang et al., cited in a review article in 2000, for the argument that the efficacy conferring the enhanced transfection activity of a delivery mixture was unknown and this would further lead to a teaching away of a generation 2 to 5 dendrimer. This line of reasoning has no relevance to the teachings of Sato et al., one because it was published a year before the findings taught by Sato and secondly because Sato et al. does conclusive show that generation 4 dendrimers can efficiently deliver oligonucleotides to cells and tissues. One of skill in the art would not consider Sato et al. as a teaching away from the use of a delivery agent comprising a dendrimer 4 agent and would not be discouraged from using dendrimers because a review article published a year prior, which did in fact teach the advantage of using a dendrimer delivery mixture, could not conclusively identify the

exact structures responsible for said enhanced activity. This is not convincing evidence that it would not have been obvious to one of ordinary skill in the art to arrive at the claimed invention after reviewing the cited prior art references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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KC
Examiner AU 1635

/Sean R McGarry/
Primary Examiner, Art Unit 1635